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Comparing Radiotherapy with Photons and Protons for Non-small Cell Lung Cancer

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Introduction: This multicentric in silico trial compares photon and proton radiotherapy for non-small cell lung cancer patients. The hypothesis is that proton radiotherapy decreases the dose and the volume of irradiated normal tissues even when escalating to the maximum tolerable dose of one or more of the organs at risk (OAR).

Methods: Twenty-five patients, stage IA-IIIB, were prospectively included. On 4D F^{18}-labeled fluorodeoxyglucose-positron emission tomography-computed tomography scans, the gross tumor, clinical and planning target volumes, and OAR were delineated. Three-dimensional conformal radiotherapy (3DCRT) and intensity-modulated radiotherapy (IMRT) photon and passive scattered conformal proton therapy (PSPT) plans were created to give 70 Gy to the tumor in 35 fractions. Dose (de-)escalation was performed by rescaling to the maximum tolerable dose.

Results: Protons resulted in the lowest dose to the OAR, while keeping the dose to the target at 70 Gy. The integral dose (ID) was higher for 3DCRT (59%) and IMRT (43%) than for PSPT. The mean lung dose reduced from 18.9 Gy for 3DCRT and 16.4 Gy for IMRT to 13.5 Gy for PSPT. For 10 patients, escalation to 87 Gy was possible for all 3 modalities. The mean lung dose and ID were 40 and 65% higher for photons than for protons, respectively.

Conclusions: The treatment planning results of the Radiation Oncology Collaborative Comparison trial show a reduction of ID and the dose to the OAR when treating with protons instead of photons, even with dose escalation. This shows that PSPT is able to give a high tumor dose, while keeping the OAR dose lower than with the photon modalities.

Key Words: In silico planning study, Multicentric trial, Lung cancer, NSCLC, Radiotherapy, Particle therapy, Dose escalation.

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Despite the advances in lung cancer treatment, it remains the number one cause of death among cancer patients in Europe and North America. Of these, 80% are categorized as non-small cell lung cancers (NSCLCs).[1,2] Different approaches in combining surgery, chemotherapy, and radiotherapy to increase tumor control and to lower complication rates are the subject of intense investigation.[3]

All over the world, proton and also carbon ion (C-ion) radiotherapy is gaining interest and popularity. In the media, it is sometimes bluntly stated that proton therapy yields the best possible treatment for every cancer patient, the arguments being solely based on the reduction of the dose administered to the healthy tissue because of the physical characteristics of charged particles. Current published comparative planning studies demonstrated the advantages in ballistic properties of particle therapy (PT) over conventional photon radiotherapy. However, these results were not sufficiently convincing, because they were often monocentric studies performed with very limited patient numbers and the treatment plans were mostly not performed according to the current clinical guidelines.

Despite a long history of proton radiotherapy, recent reviews have not shown a clear clinical evidence to implement charged PT on a large scale, mainly due to the lack of randomized controlled trials (RCTs).[4–7] However, it was concluded from a comprehensive analysis of the current data that PT was a promising treatment modality for NSCLC.[8–10] Because the cost of PT is considerably higher than conventional radiotherapy with photons, questions arise about the (cost-) effectiveness of this new technology and the need to perform RCTs.[11,12]

In response to the debate whether RCTs are needed for charged particle treatment,[13–19] a multicentric in silico clinical trial named Radiation Oncology Collaborative Comparison (ROCOCO) was initiated in 2007. It emulates a real

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clinical trial comparing photon, proton, and C-ion therapy for NSCLC, prostate, and head and neck cancer using the collaborative multicentric in silico trials in radiotherapy (MISTIR) framework (http://www.mistir.info). MISTIR uses a secured central database with virtual patient material and trial protocols comparable with the ones used in real RCTs. A set of quality assurance procedures is available to prevent, capture, and solve interoperability issues that may arise during data exchange and analysis.[20]

With the use of MISTIR and participation of some of the most experienced institutes in the field, we are able to safely explore possible clinically acceptable treatment options that may pave the way for prospective RCTs with real patients. To the best of our knowledge, no other study has been performed where 14 (refer to the list of ROCOCO consortium members) international radiotherapy centers jointly perform such an in silico trial.

This report summarizes the current results of the dosimetric comparison of three-dimensional conformal photon radiotherapy (3DCRT), intensity-modulated photon radiotherapy (IMRT), and passive scattered proton therapy (PSPT) of the NSCLC lung cohort of the ROCOCO trial. The hypothesis is that PT decreases the dose to and the volume of irradiated normal tissue while maintaining an iso-effective dose to the tumor as well as when escalating dose to the maximum tolerable dose (MTD). Consequently, the risk of side effects in the surrounding normal tissue is expected to decrease.

PATIENTS AND METHODS

Study Design

An in silico clinical trial was performed, and data from MAASTRO containing 4D F^{18}-labeled fluorodeoxyglucose (FDG)-positron emission tomography-computed tomography (PET/CT) images were deidentified and centrally stored on the secured MISTIR database as reported earlier.[20] All volumes were delineated at MAASTRO, and planning criteria were described in a predefined protocol. The participating institutes downloaded the datasets and performed treatment planning according to the provided protocol using their own clinical treatment planning system (TPS). By using the clinically commissioned TPSs, the correctness of the dose calculations was assured.

Next, the dose matrices in DICOM RT (radiotherapy extension of the *Digital Imaging and Communication in Medicine* standard) Dose format were uploaded back to the database. Then, after being checked for consistency, the dose matrices were used to calculate the dose-volume histograms (DVHs) to derive the dose metrics for the final analysis. All proton beam dose distributions were corrected to Gy(relative biological effectiveness) by applying a relative biological effectiveness factor of 1.1. The Gray unit (Gy) was used for absorbed dose reporting of both modalities.

Patient Inclusion

Between October 2007 and June 2008, 25 stage I–III NSCLC patients were included consecutively. No selection was made regarding histology, stage, or location of the tumor, resulting in a heterogeneous group of patients. An overview of the patient characteristics is given in Table 1. All patients were assumed to have a reasonable lung function (a forced expiratory volume in 1 second $\geq$50% of predicted value and a diffusing capacity of lungs for carbon monoxide [DL_{CO}] not corrected for alveolar volume $\geq$50%), so that a maximum mean lung dose (MLD) of 19 Gy could be applied.[21]

For all patients, the 4D FDG-PET/CT was used to determine the clinical staging of the tumors and individual treatment margins.

Target and OAR Definitions

Target volumes, critical organs at risk (OAR), and other normal tissues were delineated on each slice conform the literature: tumor,[22] lymph nodes,[23] and OAR (spinal cord, esophagus, lungs, and heart).[24] The spinal cord was considered to be at the inner margin of the bony spinal canal and was drawn throughout the whole CT scan. For the esophagus, the contour of the outside muscle wall was followed from the distal end of the larynx to the gastroesophageal junction. Contouring of the lungs was done using automatic delineation by thresholding on the TPS with a manual correction where needed. The heart was contoured from the apex to the origin of the large vessels, including the pericardium.

Individual peak-to-peak tumor motion was determined using the 4D CT, and delineations of the tumor and OAR were projected on the midventilation phase (50% exhale).[22] For all patients, a gross tumor volume (GTV) was defined based on the 4D FDG-PET/CT data. The GTV was defined as the primary tumor on CT and lymph nodes positive on a PET scan or proven to be positive on mediastinoscopy, transoesophageal, or transbronchial puncture. No elective nodal irradiation was performed. Syngo TrueD (Siemens Medical Solutions, Malvern, PA) was used to automatically define the PET positive areas by using a pathology-validated source-to-background method.[25–27]

The clinical target volume (CTV) was defined as the GTV with a margin of 5 mm. Next, the individual, anisotropic planning target volume (PTV) margins for photons were calculated in three directions (cranial-caudal, left-right, and anterior-posterior) using a margin recipe (refer to the Appendix, Eq. A1). For protons, the margins from CTV to PTV are determined differently, to incorporate a lateral smearing factor and range uncertainties (refer to the treatment planning section hereafter and the Appendix).

Treatment Planning

Treatment planning was performed for 3DCRT, IMRT, and PSPT at MAASTRO, the Netherlands Cancer Institute, and the Massachusetts General Hospital (MGH), using XiO (v4.34, CMS Software, St. Louis, MO), Pinnacle (ADAC Laboratories, Milpitas, CA), and a modified proton enabled version of XiO (v4.2.1), respectively. For the photon dose calculations, a multigrid superposition algorithm[28] or equivalent was used to account for tissue heterogeneity. Proton dose calculations were performed using a modified version of the XiO pencil beam algorithm with one-dimensional density corrections. The dose matrices, with a $3 \times 3 \times 3$-mm^3 grid

TABLE 1. Patient Characteristics of the Datasets Showing Histology, TNM Classification, Staging, Top–Top Amplitudes of the Tumor Measured on the 4D PET/CT Scan, and the Derived Anisotropic Margins for Photons

				Amplitude (mm)			CTV to PTV Margin (mm)		
Patient	Histology	TNM	Stage	CC	LR	AP	CC	LR	AP
1	Squamous	T3N2M0	IIIA	20	5	10	10	6	8
2	Adeno	T2N3M0	IIIB	4	3	9	8	6	8
3	Adeno	T2N2M0	IIA	8	3	5	8	6	7
4	Squamous	T4N0M0	IIIB	3	2	2	7	6	7
5	Squamous	T2N1M0	IIB	8	4	6	8	6	7
6	Large cell	T4N2M0	IIIB	5	2	3	8	6	7
7	Squamous	T4N0M0	IIIB	14	3	4	9	6	7
8	Large cell	T1N2M0	IIIA	17	10	20	10	7	10
9	Large cell	T4N3M0	IIIB	17	3	5	10	6	7
10	Large cell	T2N2M0	IIIA	8	2	2	8	6	7
11	Large cell	T2N3M0	IIIB	13	2	1.5	9	6	7
12	Large cell	T1N3M0	IIIB	4.5	3	3	8	6	7
13	Large cell	T1N2M0	IIIA	7	2	2	8	6	7
14	Adeno	T2N2M0	IB	3	2	2	7	6	7
15	Squamous	T2N0M0	IIIA	11	3	4	9	6	7
16	Adeno	T4N2M0	IIIB	6	3.5	3	8	6	7
17	Large cell	T2N3M0	IIIB	6	2	2	8	6	7
18	Squamous	T1N0M0	IA	4	5	6	8	6	7
19	Squamous	T2M0N0	IB	1	1	1	7	6	7
20	Large cell	T2N0M0	IB	5	2	2	8	6	7
21	Large cell	T1N2M0	IIIA	10	7	3	8	6	7
22	NSCLC NOS	T4N3M0	IIIB	4.5	2.5	4	8	6	7
23	Adeno	T1N1M0	IIA	5	4	2	8	6	7
24	NSCLC NOS	T4N3M0	IIIB	4.5	6	4	8	6	7
25	Large cell	T2N2M0	IIIA	3	1	1.5	7	6	7

CC, cranial-caudal; LR, left-right; AP, anterior-posterior; Squamous, squamous cell carcinoma; Adeno, adenocarcinoma; Large cell, large cell carcinoma; NSCLC NOS, non-small cell lung cancer not otherwise specified; CTV, clinical target volume; TNM, tumor, node, metastasis; PET, positron emission tomography; CT, computed tomography.

size, were uploaded in DICOM RT Dose format onto the secured central server.

For all modalities, the prescribed dose (PD) was 70 Gy to the PTV in 2 Gy fractions, once a day. Criteria for minimum and maximum dose were defined according to a modified ICRU 50 protocol[29]: $D_{98} \geq 95\%$ and $D_2 \leq 107\%$ of the PD. The maximum dose (D_2) to the spinal cord and esophagus equaled 54 and 80 Gy, respectively, using 2 Gy fractions, independent of the volume. For the lungs, the MLD was limiting to a biologically equivalent dose in 2 Gy fractions (EQD_2) of 19 Gy. The MLD volume was defined as the volume of both lungs minus the GTVs. For the heart, three DVH metrics were defined: $V_{60} < 33\%$, $V_{45} < 66\%$, and $V_{40} < 100\%$.

Two plans were created per patient. First, a fixed PD of 70 Gy to the tumor was used. Next, plans were upscaled or downscaled by adapting the fraction dose to fulfill all criteria of the OARs. The mean CTV dose was then reported as MTD. A maximum fraction dose of 4 Gy was considered, resulting in an EQD_2 to the tumor of 163 Gy. Table 2 summarizes the physical and corresponding EQD_2-planning criteria for the target and OAR.

TABLE 2. Conversion Table Between EQD_2 and Physical Dose for Target and OAR

Structure of Interest	α/β (Gy)	Criterion	EQD_2 (Gy)	Physical Dose at 35 Fractions (Gy)
PTV	10	D_2	163	140
Lungs	3	MLD	≤19	Depends on distribution[a]
		D33%	60	63
Heart	3	D67%	45	51
		D100%	40	46
Esophagus	3	D_2	80	77
Spinal cord	2	D_2	54	59

[a] The EQD_2 of the MLD was calculated using the full 3D physical dose distribution and recalculating the equivalent dose at each point.

EQD_2, equivalent dose in 2 Gy fractions; OAR, organs at risk; MLD, mean lung dose; PTV, planning target volume.

Photons

3DCRT plans were created at MAASTRO as per the clinical guidelines. The plans consisted of multiple, optimized coplanar beams using a multileaf collimator and wedges to shape the dose conformally to the target. In many

cases, additional small beams from the same directions were used with limited dose to "pull" the isodoses around the PTV. The energy of the photon beams was almost always 10 MV.

IMRT plans were created at the Netherlands Cancer Institute consisting of six to ten 10-MV beams. The beam configuration was mainly coplanar with a few exceptions. The collimator was rotated to fit best the shape of the target and OARs. For the optimization, the criteria as given above were used in combination with constraints to some additional structures to control the dose to certain areas or force rapid dose fall-off around the PTV. Initial optimization was done using 30 segments with 25-cm^2 size. When needed, the number of segments was increased to 50, while the segment size could be decreased to 12 cm^2.

Protons

The passive-scattered proton plans were planned at MGH using the XiO TPS. Each plan consisted of at least two (preferably three) beam directions to spread out the dose to normal tissues. Using a midventilation CT scan of the tumor, first, for each beam, an aperture, range compensator, range and modulation were chosen to conform the 95% isodose level as closely as possible to the target, that is, the CTV. Second, margins were applied to the aperture, the range compensator, and both the range and modulation width taking setup errors and breathing motion into account.

Beam directions that are parallel to density interfaces such as the lung and mediastinum were avoided because of the large range uncertainties even for small setup errors. Because of the low density of inflated lung (e.g., 0.25 g/cm^3), overshoot due to range uncertainties and applied smearing results in a substantial volume of lung receiving full dose for a given beam direction. Therefore, the beam angles were intentionally aimed toward the mediastinum. Refer to the Appendix for a detailed description of the proton planning process.

Analysis

To minimize the uncertainty in the analysis, all the DVH metrics (refer to Table 3 and 4) were centrally derived by MAASTRO from the 3D-dose matrices. Because the PTV is different for photon and proton modalities due to different margin algorithms, we chose the CTV for target comparison. We compared integral doses (ID), defined as the mean dose to the imaged patient, as dosimetric estimate for normal tissue toxicity differences between the three modalities.

For an estimation of the differences in the therapeutic windows of the treatment modalities, we introduced surrogate therapeutic indices (TIs) for the lungs, esophagus, and spinal cord. These were derived by dividing the mean dose to the target by the essential dose metric of the structure. For example, for the lungs, this would result in a TI_{MLD} defined by the MTD over the MLD.

To quantitatively assess the differences in conformity of the different treatment modalities, various indices have been proposed in the literature.[30] Because we wanted to compare the different treatment modalities based on target coverage and unwanted dose to the noncritical as well as the critical normal tissue (OARs), we used a "conformation number" (CN) as defined by:

$$CN = \frac{CTV_{95}}{CTV} \times \frac{CTV_{95}}{V_{95}} \quad (1)$$

where CTV_{95} and V_{95} are the volume of the CTV and the overall volume, respectively, receiving minimally 95% of the target dose. Refer to the Appendix or Ref. 31 for a more elaborate description.

To investigate the volume of the low-dose region in the patient, a sparing index ($SPIN_{50/10}$) was used[32]:

$$SPIN_{50/10} = 1 - V_{10}^{50} \quad (2)$$

where V_{10}^{50} is the ratio of the volume of tissue that receives between 10 and 50% of the PD to the irradiated volume. The irradiated volume was defined as the volume of tissue that receives at least 0.5% of the PD.

For both CN and $SPIN_{50/10}$, a value of 1 would indicate a perfect, theoretical dose distribution solely around the target and none in the healthy tissue.

Two-tailed, signed-rank Wilcoxon tests were calculated using SPSS (version 15, Chicago, IL) and Matlab (The MathWorks, Natick, MA) to determine the significance of pairwise differences between modalities. The values of p less than 5/3% were considered significant.

We must note that, in general, some of the mentioned metrics are not suitable as absolute measures of plan quality or treatment modality performance. For instance, when considering volumes of OAR, they can depend on the imaged patient volume (e.g., spinal cord) and of course the anatomical differences of the patients. In this study, we used these metrics in a relative way and compared these metrics pairwise as indicated above. This way, a statement of better plan quality is possible.

RESULTS

Of the 25 included patients for the iso-effective protocol (Table 1), all were planned with 3DCRT and IMRT and 23 with PSPT. Two patients with tumors located very cranially were excluded from proton planning. In real life, these patients would not be treated with PSPT because of the limited beam directions possible and because of remaining range uncertainties due to accuracy in the positioning of the arms. Because of the pairwise analysis, we report on the remaining 23 corresponding datasets.

In Figure 1, mid-PTV dose distributions are shown for three typical cases. In general, IMRT showed a more conformal dose compared with 3DCRT and both showed a fairly large low-dose region outside the target. PSPT showed its typical clear-edged beams with no exit dose. Figure 2 shows the DVHs for one of the patients (#2).

When irradiating with protons, it was found (Table 3) that, while prescribing the same dose to the target, the average ID was significantly lower than for 3DCRT (59%, $p < 0.001$) and IMRT (43%, $p < 0.001$). Except for V_{30Gy}, all lung volume metrics were significantly higher for photons than for protons. The average MLD was significantly higher

TABLE 3. DVH Metrics of the Photon and Proton Treatment Plans for the Prescribed and Maximum Tolerable Dose

	PD = 70 Gy			MTD		
	Photons		Protons	Photons		Protons
	3DCRT	IMRT	PSPT	3DCRT	IMRT	PSPT
Target (CTV)						
D_{mean}	71.3 (1.0)[a]	70.7 (0.9)	70.3 (0.7)	75.0 (22.2)	81.5 (20.8)	75.0 (21.2)
D_2	73.9 (1.4)[a]	73.1 (1.9)[a]	72.0 (0.8)	77.6 (22.2)	84.2 (21.6)	76.7 (21.4)
D_{98}	68.9 (1.1)	68.7 (1.1)	68.7 (1.0)	72.6 (22.2)	79.2 (20.5)	73.3 (21.0)
CN	0.25 (0.07)	0.38 (0.10)[a]	0.25 (0.08)	0.25 (0.07)	0.38 (0.10)[a]	0.25 (0.08)
Patient						
ID	11.0 (5.4)[a]	9.9 (4.4)[a]	6.9 (3.9)	10.2 (3.2)[a]	10.6 (3.7)[a]	6.8 (3.1)
$SPIN_{50-10}$	0.70 (0.05)[a]	0.72 (0.04)[a]	0.61 (0.09)	0.71 (0.05)[a]	0.73 (0.04)[a]	0.62 (0.09)
TI_{ID}	8.6 (5.2)[a]	9.1 (5.4)[a]	15.3 (11.5)	8.6 (5.2)[a]	9.1 (5.4)[a]	15.3 (11.5)
Organs at risk						
Lung						
V_{30Gy}	21.0 (9.8)[a]	16.3 (7.7)	16.8 (8.9)	20.3 (7.6)[a]	17.7 (6.6)	16.7 (8.1)
V_{20Gy}	27.1 (12.6)[a]	23.4 (10.2)[a]	20.5 (10.4)	26.4 (9.5)[a]	25.0 (9.3)[a]	20.2 (10.2)
V_{13Gy}	37.0 (17.5)[a]	32.1 (11.8)[a]	23.3 (12.0)	36.1 (12.8)[a]	34.1 (10.2)[a]	23.1 (11.5)
V_{5Gy}	53.1 (17.0)[a]	56.9 (12.9)[a]	27.5 (13.9)	53.2 (15.5)[a]	59.1 (10.2)[a]	27.5 (13.7)
MLD	18.9 (7.3)[a]	16.4 (5.5)[a]	13.5 (6.2)	18.2 (4.1)[a]	17.9 (4.1)[a]	13.6 (5.6)
TI_{MLD}	4.5 (1.9)[a]	4.9 (2.0)[a]	6.8 (3.9)	4.5 (1.9)[a]	4.9 (2.0)[a]	6.8 (3.9)
Spinal cord						
D_2	40.0 (21.4)	42.6 (9.6)	37.9 (23.2)	37.0 (17.1)	46.8 (6.3)[a]	35.5 (18.1)
TI_{D2}	6.7 (15.2)	1.8 (0.7)[a]	31.7 (105)	6.8 (15.7)	1.8 (0.7)[a]	52.1 (198)
Esophagus						
D_2	65.0 (15.7)	64.7 (15.8)	63.6 (17.9)	64.5 (13.8)	70.3 (11.0)	65.7 (17.3)
D_{mean}	28.3 (13.9)[a]	26.0 (12.1)	24.4 (13.7)	26.3 (9.4)[a]	27.5 (11.1)[a]	23.7 (11.7)
V_{55Gy}	31.0 (20.2)	26.4 (18.1)	28.3 (19.1)	22.0 (16.2)	27.3 (17.3)	22.2 (16.7)
V_{35Gy}	38.3 (22.7)[a]	34.9 (19.9)	35.3 (20.3)	37.8 (20.2)	37.0 (17.4)	35.3 (18.7)
TI_{D2}	1.3 (0.8)	1.3 (0.7)	2.0 (4.1)	1.3 (0.8)	1.3 (0.7)	2.0 (4.1)
Heart						
D_{mean}	15.3 (11.6)[a]	14.3 (10.3)[a]	7.6 (7.2)	14.3 (9.5)[a]	15.3 (10.0)[a]	7.5 (7.1)
V_{65Gy}	4.4 (5.5)[a]	2.3 (3.3)[a]	3.0 (4.0)	2.1 (3.0)	2.0 (2.9)	2.3 (4.2)
V_{45Gy}	13.3 (13.3)[a]	9.1 (9.3)[a]	6.2 (6.5)	10.1 (9.6)[a]	9.6 (8.5)[a]	6.1 (6.3)
V_{40Gy}	15.1 (14.5)[a]	11.5 (11.7)[a]	7.2 (7.2)	12.4 (10.8)[a]	12.4 (10.9)[a]	7.2 (7.1)
V_{30Gy}	19.5 (17.2)[a]	17.0 (16.1)[a]	12.0 (13.4)	18.5 (15.1)[a]	18.5 (15.4)[a]	11.7 (13.1)
V_{20Gy}	27.0 (23.7)[a]	25.3 (22.2)[a]	15.1 (15.6)	26.5 (19.8)[a]	27.6 (21.3)[a]	15.0 (15.4)
V_{10Gy}	40.9 (31.8)[a]	41.0 (31.9)[a]	18.1 (17.5)	40.7 (30.6)[a]	45.0 (33.4)[a]	18.1 (17.3)
TI_{Dmean}	13.1 (16.8)[a]	13.0 (14.9)[a]	572 (2074)	13.1 (16.8)[a]	13.0 (14.9)[a]	572 (2074)

Data for the target and the organs at risk are given as mean physical dose values with the standard deviation in parenthesis. [a]Significant differences ($p < 0.0167$) of the photon vs. the proton results.

PD, prescribed dose; MTD, maximum tolerable dose; 3DCRT/IMRT/PSPT, 3D conformal photon/intensity-modulated photon/3D passive scattered proton radiotherapy; Dx, dose (Gy) given to x% (or mean) of the volume; CN, conformation number (Eq. 4); ID, integral dose in Gy; TIy, therapeutic index (MTD/y); VzGy, percent volume of the total organ's volume that receives more than z Gy (for the lung results, the volume was taken as both lungs minus the PTV for photons); MLD, mean lung dose in Gy (lung volume taken as both lungs minus the GTVs); CTV, clinical target volume.

for 3DCRT (40%; $p < 0.001$) and IMRT (21%; $p < 0.001$) when compared with PSPT. This resulted in a significantly higher $TI\text{-}_{MLD}$ for PSPT when compared with 3DCRT (51%, $p < 0.001$) or IMRT (39%, $p < 0.001$).

For the spinal cord and esophagus, the average maximum doses (D_2) did not differ significantly between the three modalities. The average mean dose to the esophagus was slightly larger for 3DCRT (16%, $p < 0.001$) and IMRT (6.6%, $p = 0.02$) than for PSPT. All average heart metrics were significantly lower for protons when compared with photons, except for the V_{65Gy}, which was 23% lower for IMRT ($p = 0.002$). The average TI_{Dmean} for both photon modalities was 44 times lower ($p < 0.001$) than for protons.

With respect to the conformity of the three different modalities, it was shown that IMRT had an average 50% higher CN ($p < 0.001$), while 3DCRT scored equally compared with PSPT. Also, the $SPIN_{50-10}$ was significantly worse for PSPT than for 3DCPT and IMRT: 0.61 ± 0.09 versus 0.70 ± 0.05 ($p < 0.002$) and 0.72 ± 0.04 ($p < 0.001$), respectively.

After upscaling or downscaling all plans to clinically acceptable MTD by fulfilling all planning criteria, the PD to

TABLE 4. DVH Metrics of the Photon and Proton Treatment Plans, Split for Plans Where all Modalities Simultaneously Could Escalate the Dose to the Tumor and Some That Did Not

	One or More Modalities Had to De-escalate (n = 13)			All Modalities Could Escalate (n = 10)		
	Photons		Protons	Photons		Protons
	3DCRT	IMRT	PSPT	3DCRT	IMRT	PSPT
Target (CTV)						
D_{mean}	66.7 (22.8)	76.6 (19.2)	64.6 (10.1)	85.8 (17.0)	87.9 (22.0)	88.5 (24.5)
D_2	69.4 (22.7)	79.0 (19.6)	66.2 (10.5)	88.3 (17.3)	91.1 (23.2)	90.4 (24.6)
D_{98}	64.3 (22.8)	74.4 (19.0)	63.1 (10.0)	83.5 (16.7)	85.6 (21.7)	86.4 (24.5)
CN	0.26 (0.08)	0.41 (0.12)[a]	0.28 (0.10)	0.23 (0.06)	0.34 (0.07)[a]	0.23 (0.05)
Patient						
ID	11.8 (3.1)[a]	12.3 (3.7)[a]	8.1 (3.1)	8.2 (2.1)[a]	8.3 (2.1)[a]	5.0 (2.0)
$SPIN_{50-10}$	0.69 (0.05)[a]	0.72 (0.04)[a]	0.63 (0.08)	0.74 (0.04)[a]	0.74 (0.03)[a]	0.60 (0.10)
TI_{ID}	6.7 (5.4)[a]	7.4 (5.4)[a]	11.5 (11.6)	11.1 (3.9)[a]	11.4 (4.6)[a]	20.2 (9.9)
Organs at risk						
Lung						
V_{30Gy}	22.6 (8.4)	18.8 (6.8)	18.8 (9.2)	17.2 (5.4)	16.4 (6.4)[a]	13.9 (5.9)
V_{20Gy}	30.1 (9.9)[a]	26.9 (9.7)	23.4 (11.2)	21.6 (6.7)[a]	22.5 (8.5)[a]	16.1 (7.2)
V_{13Gy}	40.2 (14.5)[a]	36.5 (10.3)[a]	27.1 (12.5)	30.8 (7.9)[a]	31.0 (9.6)[a]	17.8 (7.8)
V_{5Gy}	60.4 (15.7)[a]	63.7 (7.6)[a]	32.3 (15.1)	43.9 (9.4)[a]	53.2 (10.5)[a]	21.4 (9.0)
MLD	19.8 (3.6)[a]	19.5 (3.3)[a]	15.4 (5.7)	16.1 (3.8)[a]	15.8 (4.2)[a]	11.3 (4.8)
TI_{MLD}	3.6 (1.8)[a]	4.2 (1.9)[a]	4.9 (2.5)	5.6 (1.5)[a]	5.9 (1.9)[a]	9.2 (4.2)
Spinal cord						
D_2	42.3 (16.2)	48.3 (4.8)	44.7 (13.2)	30.1 (16.5)	44.8 (7.7)[a]	23.6 (17.1)
TI_{D2}	6.9 (19.5)	1.6 (0.37)	1.7 (0.87)	6.7 (9.5)	2.1 (0.9)[a]	117 (295)
Esophagus						
D_2	59.0 (9.5)	69.8 (11.5)	61.2 (19.8)	71.7 (15.6)	71.0 (10.7)	71.5 (11.9)
D_{mean}	31.2 (7.6)	33.1 (10.7)	29.8 (10.7)	20.0 (7.9)[a]	20.2 (6.6)[a]	15.9 (7.7)
V_{55Gy}	25.5 (18.5)	35.1 (17.1)	26.8 (19.0)	17.6 (12.0)	17.2 (11.8)	16.3 (11.6)
V_{35Gy}	49.5 (16.3)	45.5 (17.7)	45.5 (17.2)	22.5 (13.5)	26.0 (9.1)[a]	22.0 (10.6)
TI_{D2}	1.2 (0.78)	1.2 (0.81)	2.5 (5.4)	1.3 (0.8)	1.3 (0.59)	1.3 (0.72)
Heart						
D_{mean}	17.3 (9.3)[a]	18.9 (9.8)[a]	9.6 (7.9)	10.4 (8.7)[a]	10.5 (8.5)[a]	4.7 (5.0)
V_{65Gy}	1.3 (2.5)	2.2 (3.6)	2.5 (5.4)	3.1 (3.5)	1.7 (1.7)	2.0 (2.1)
V_{45Gy}	10.9 (9.1)	12.5 (9.0)[a]	7.8 (7.3)	9.0 (10.6)[a]	5.7 (6.1)	4.0 (4.0)
V_{40Gy}	14.3 (10.1)	16.3 (11.5)[a]	9.2 (8.2)	10.0 (11.6)[a]	7.2 (7.9)[a]	4.6 (4.6)
V_{30Gy}	23.3 (14.9)	24.1 (15.6)[a]	15.5 (15.3)	12.2 (13.4)[a]	11.3 (12.2)[a]	6.7 (7.7)
V_{20Gy}	33.2 (19.2)	35.0 (21.0)[a]	19.8 (17.2)	17.8 (17.8)[a]	17.9 (18.3)[a]	8.8 (10.5)
V_{10Gy}	53.2 (31.8)[a]	56.1 (31.6)[a]	23.6 (19.0)	24.4 (20.7)[a]	30.5 (31.4)[a]	10.9 (12.1)
TI_{Dmean}	11.3 (19.8)[a]	9.0 (12.6)[a]	941 (2744)	15.4 (12.3)[a]	18.0 (16.8)[a]	91.5 (126.8)

Data for the target and the organs at risk are given as mean physical dose values with the standard deviation in parenthesis. [a]Significant differences ($p < 0.0167$) of the photon vs. the proton results.

PD, prescribed dose; MTD, maximum tolerable dose; 3DCRT/IMRT/PSPT, 3D conformal photon/intensity-modulated photon/3D passive scattered proton radiotherapy; Dx, dose (Gy) given to x% (or mean) of the volume; CN, conformation number (Eq. 4); ID, integral dose in Gy; TIy, therapeutic index (MTD/y); VzGy, percent volume of the total organ's volume that receives more than z Gy (for the lung results, the volume was taken as both lungs minus the PTV for photons); MLD, mean lung dose in Gy (lung volume taken as both lungs minus the GTVs); CTV, clinical target volume.

the tumor of 70 Gy could be increased for 52, 83, and 61% of the patients for 3DCRT, IMRT, and PSPT, respectively (Table 3). The other patients received the PD or lower. Refer to Figure 2 for DVHs of such a case (#2).

The mean MTD was 8.6% higher for IMRT when compared with PSPT, although this was not significant. The 3DCRT MTD did not differ from PSPT. The ID was higher again for both photons modalities when compared with protons ($p = 0.005$). Once more, all lung volume metrics were significantly higher for photons than for protons, except for V_{30Gy}. The average MLD was significantly higher for 3DCRT (34%; $p < 0.001$) and IMRT (32%; $p < 0.001$) when compared with PSPT.

For the spinal cord, the average maximum dose (D_2) was 42% higher for IMRT than for PSPT ($p = 0.005$). The average mean dose to the esophagus was larger for 3DCRT (11%, $p = 0.007$) and IMRT (16%, $p = 0.005$) than for PSPT. All average heart metrics were significantly lower for

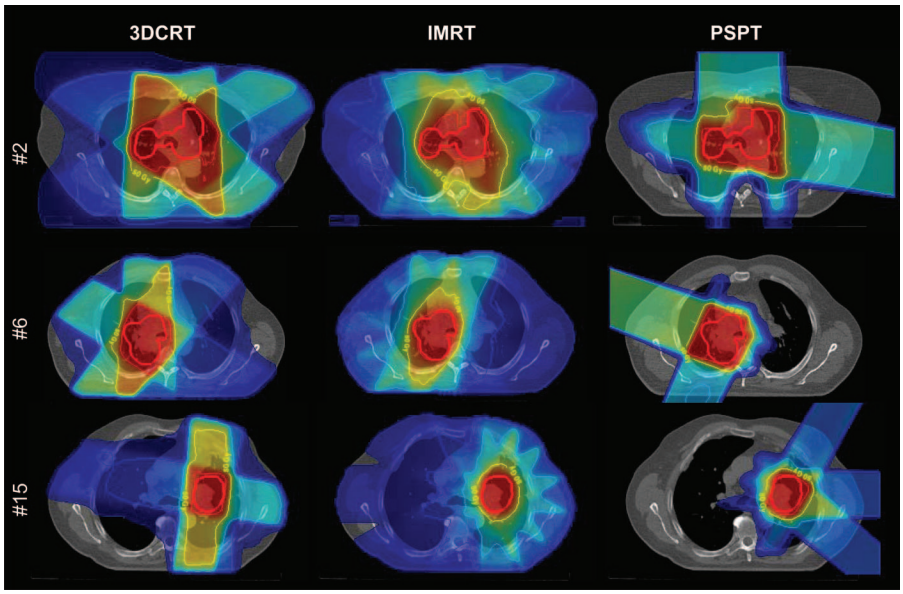

FIGURE 1. Comparison of dose distributions of three-dimensional conformal photon radiotherapy (3DCRT), intensity-modulated radiotherapy (IMRT), and passive scattered conformal proton therapy (PSPT) treatment plans (columns) for three cases (rows). The target is shown (red) with isodose lines of 1, 10, 25, 50, and 67 Gy.

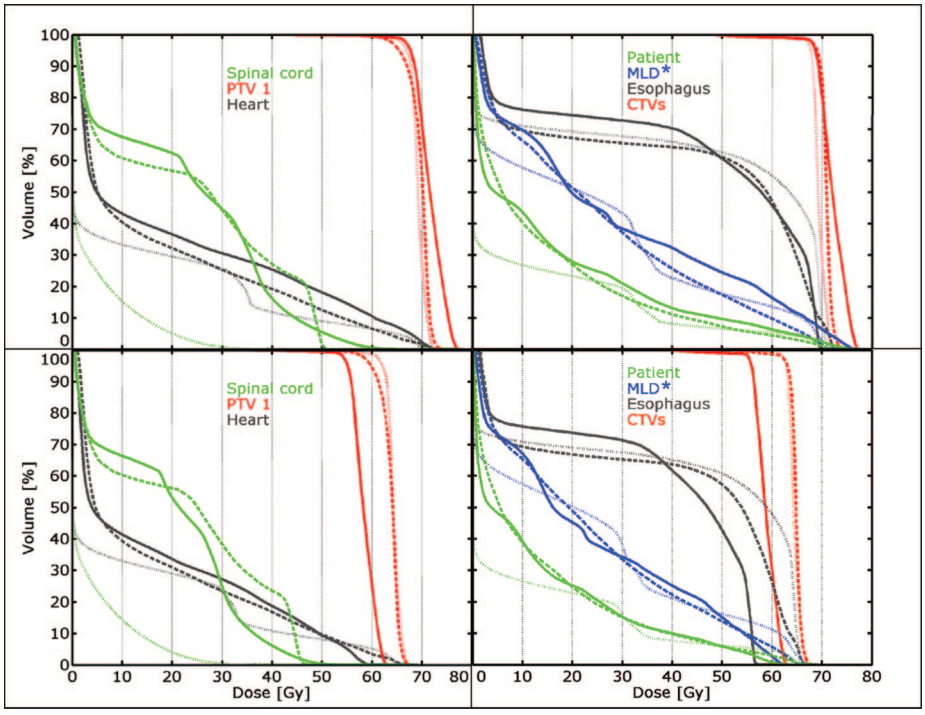

FIGURE 2. Dose-volume histograms (DVHs) for patient #2 where the prescribed dose of 70 Gy resulted in exceeding the critical mean lung dose (MLD) level (upper). Lowering the dose to the maximum tolerable dose resulted in lower DVH (bottom), showing larger under-dosage for three-dimensional conformal photon radiotherapy (solid) than for intensity-modulated radiotherapy (dashed) or passive scattered conformal proton therapy (dotted). *MLD refers to the DVH of both left and right lung volumes minus the gross tumor volume.

protons when compared with photons, except for the V_{65Gy}, which did not differ significantly.

Because of the rescaling of the dose matrices, the DVH metrics that are based on relative dose levels or ratios typically do not change. One exception is the TI_{D2} for the spinal cord where the accuracy of the D_2 is limited by some very small irradiated volumes.

For 10 patients (two stage I, one stage II, and seven stage III), all modalities could escalate the dose to an MTD of approximately 87 Gy (Table 4). The average ID was about 65% higher for photons than for protons ($p = 0.005$). The MLD was 42% higher for 3DCRT ($p = 0.007$) than for PSPT, whereas it was 40% higher for IMRT ($p = 0.005$). The TI_{ID} and TI_{MLD} were nearly double of those of the nonescalated group. For the spinal cord, the maximum dose was 90% higher for IMRT than for PSPT ($p = 0.005$). For the esophagus, the maximum dose was approximately 71.5 Gy for all modalities. The mean dose to the heart for photons was double the dose for protons, whereas the V_{40Gy} was 117% higher for 3DCRT ($p = 0.013$) and 57% higher for IMRT ($p = 0.013$) than for PSPT.

Further subgroup analysis based on tumor volume, location, or stage did not provide new information and is omitted from this report.

DISCUSSION

With the first results from 23 cases of the lung cohort of the ROCOCO trial, we have shown that for the treatment of NSCLC, stage I to III, proton radiotherapy is superior to photon radiotherapy, in terms of reduction of the normal tissue dose. Based on the ID, an absolute improvement of 3 to 4 Gy was seen for protons, resulting in an improved therapeutic index in the order of 15 compared with 9.

In the current literature, with a few exceptions,[33–35] 10 or less patients were used in the published treatment planning comparisons. Furthermore, in most of the published articles, it is unclear what the selection criteria were of the included patients, possibly introducing selection bias. Publications dating before 2000 did not consider intensity-modulated radiation therapy as a modality for photon therapy or intensity-modulated PT. By using a multicentric approach, with consensus on a predefined protocol and a relatively large amount of patients, a high level of confidence was achieved in this study as the established clinical experience of the participants was used.

In this study, we found that the average V_{20Gy} of the lungs were lower for both IMRT and PSPT compared with 3DCRT (16.3, 16.8, and 21%, respectively). Regarding the MLD, it was found that this was lowest for PSPT (13.5 Gy) when compared with 3DCRT (18.9 Gy) or IMRT (16.4 Gy). Previous research has shown that the V_5 of the lungs was also associated with lung toxicity.[36] This study showed that the V_5 for protons was less than half the value for both photon modalities.

Although the average maximum dose to the spinal cord did not significantly change between all three modalities, it was shown that the average of the corresponding individual therapeutic index was significantly higher for PSPT (31.7) than for IMRT (1.8). This indicates that there are a few outliers present in the derived metrics.

Furthermore, the maximum dose to the esophagus was nearly equal for all three modalities. The V_{55Gy} appeared to be lowest for IMRT (26.4%). When considering the V_{35Gy}, however, it was equal for IMRT and PSPT (35%). The mean heart dose for photons was nearly double the dose of protons, whereas the V_{40Gy}, which is known for its correlation to heart toxicity, was 110 and 60% higher for 3DCRT and IMRT, respectively, than for PSPT.[24]

It is expected that the lower dose to the normal tissues with proton therapy will lower the probability of normal tissue complications and result in a better quality of life in an iso-effective setting. Clinical validated models have been published showing this for a variety of acute and late toxicities.[37–40]

Radiation therapy is known for its statistically significant increased risk of secondary malignancies.[41] The hypothesis of reduced late side effects with proton therapy has been investigated intensely and tends to be correctly supported, although large uncertainties in the relative biological effect, among others, remain.[42–46] In addition, improvements in the treatment delivery equipment further reduce the amount of secondary neutron production, which is the main contributor to the scattered dose to the normal tissue.[47–49] Although the occurrence of secondary tumors for lung cancer patients could be considered irrelevant due to the short life expectancy, the expected reduced carcinogenic risk should be mentioned with respect to the changing NSCLC population and overall treatment improvements.

Another advantage of the small low-dose volume and limited number of beams for protons is that it offers the opportunity to better reirradiate for loco-regional metastasis. The increased therapeutic ratios showed that there is a room for iso-toxic dose escalation with protons for certain patients. A unicentric study including a selection of 15 stage III patients has shown that dose escalation from 63 to 74 Gy was possible with PSPT while keeping normal tissue toxicity lower than with 3DCRT or IMRT.[33] Early results of a subsequent phase II trial show that a dose prescription to 74 Gy is well tolerated with proton therapy.[50]

The current report predicts that this still holds for MTDs exceeding these levels with about 10 Gy. For 40% of the patients, dose escalation was possible to a mean level of more than 85 Gy for all modalities. With dose levels of such ablative magnitude, while still maintaining the dose to the OAR below a toxic level, it is expected that local tumor control will significantly be increased and consequently will lead to a further improved survival with acceptable toxicity. A phase II dose escalation trial is currently being performed to investigate sub-boosting of high FDG-PET uptake regions to such high doses with IMRT.[51] PSPT will not be a part of this trial because range uncertainties make it nearly impossible to ensure a certain limited dose to an OAR by means of forward planning.

When the treatment plans of the three modalities were evaluated for possible dose escalation, it showed that sometimes the dose could be increased for one modality while it had to be lowered for another. The fact that this heterogeneity cannot be predicted beforehand makes generalization of the achieved results difficult. This raises the demand for an individualized approach when trying to classify eligibility of a patient to receive proton therapy instead of less expensive photon therapy (see Slides, Supplemental Digital Content 1, http://links.lww.com/JTO/A179, which show a Proton therapy reimbursement decision tree for the Netherlands and Figures 1 and 2).

The performance of the CN and $SPIN_{50-10}$ is worse when using PSPT instead of 3DCRT or IMRT. The error margins that are needed to compensate in depth and width and the fact that only two to three beams are used to generate an irradiated volume that exceeds the PTV used for photons. However, even though PSPT suffers from these disadvantages, the dose to the normal tissues remains much lower than for 3DCRT and IMRT. This indicates that the use of conformity and dose spill indices is useful for plan comparison but they do not cover the full plan evaluation and cannot by themselves indicate prevalence of either treatment modality.

One might argue that PSPT is not the latest and most advanced type of PT, but despite this, the current results show that it is favorable in terms of normal tissue dose reduction when compared with photon radiation therapy. It could be argued that if results were derived from modern scanning proton beam therapy, the dose distributions could improve due to reduced secondary neutron production[47,52] and improved conformity. Recent publications show indeed that intensity-modulated proton therapy (IMPT) is able to lower the dose to the normal tissue and allows dose escalation up to 88 Gy for a selection ($n = 20$) of extensive stage IIIB NSCLC patients.[53]

For stage I NSCLC patients, stereotactic radiotherapy is increasingly used. In a meta-analysis, it was previously found that proton therapy results in similar survival rates as stereotactic body radiation therapy.[9] In another publication, the influence of different breathing suppression methods was investigated in a PSPT, IMPT, and stereotactic radiotherapy treatment planning study.[34] Both proton techniques were superior in sparing the normal tissue when compared with SBRT. However, the differences were small, and improved local control rates needed clinical validation. More recent publications report that PSPT and especially IMPT do benefit from the superior dose distribution and result in a significant normal tissue sparing.[54,55]

Within our current dataset, there were individual cases (stage IIA and IIIA) that reached MTD levels well above 100 Gy with any of the three modalities. Subgroup analysis did not show a significantly higher proton dose level for tumors with different staging or tumor size. This again indicates that the best treatment modality could be difficult to predict beforehand and should be investigated on an individual basis. Future research should preferably include other modalities such as IMPT or even C-ion radiotherapy. The ROCOCO consortium is considering to do so with the datasets and methods presented here. However, up to this date, we have not found a reliable method to calculate treatment plans for these new treatment modalities when delivered to moving lung tumors.

The evidence for the dosimetric improvements of PT is still hampered by sufficient clinically validated results.[13–19,56] However, it is possible to use highly accurate dose calculations and well-established predictive radiobiological models[57–59] in an in silico approach as a surrogate to determine the (cost-)effectiveness of PT with sufficient reliability. A signal in that direction is the fact that the in silico approach used in this study was acknowledged and justified by the Dutch Health Care Insurance Board (CVZ)[60] as a vital supplement to prospective RCTs.

Recently published studies show the potential cost-effectiveness of PT in NSCLC. However, they emphasize the uncertainty in determining this and the probability of making a wrong decision with regard to establishing a particle center.[61] It is, therefore, important that when new evidence becomes available, reassessment of the (cost-)effectiveness of PT in lung cancer should be carried out. Next, the theoretical benefit should be confirmed by clinical evidence from well-designed prospective studies. We argue that the results of in silico trials such as the one currently presented aid to choose the most relevant areas of research for RCTs involving proton therapy.

CONCLUSIONS

By using an in silico approach, we found that while maintaining a good coverage of the target, proton radiotherapy significantly reduced the dose to the normal tissue, as indicated by a lower ID, when compared with conventional or intensity-modulated photon therapy for NSCLC patients.

Furthermore, the presented data show that dose escalation is possible and that an increased local tumor control can be expected, hence improving survival. We believe that carefully designed RCTs should now be performed to validate these results.

The current findings provide an incentive to investigate other tumor sites and modalities such as C-ion radiotherapy in an in silico set-up. For NSCLC patients, the possibilities of hypofractionated delivery schedules could be investigated as well. Finally, because investment costs are high, it would be valuable to investigate whether PT can be considered cost-effective.

APPENDIX

Margin Recipe

The clinical target volume (CTV) was defined as the GTV with a margin of 5 mm. Next, the individual, anisotropic planning target volume (PTV) margins for photons (Eq. A1) were calculated in three directions (CC, LR, and AP) using a margin recipe.[62]

$$M_{PTV} = 2.5 \cdot \sum + 0.7\sqrt{\sigma^2 + A^2/8} \qquad \text{(A1)}$$

with Σ the overall standard deviation (SD) of the systematic errors, σ the overall SD of the random errors and A the peak-to-peak amplitude of the tumor. We used the systematic and random set-up errors as determined in MAASTRO's clinical setting. Because the midventilation CT was used, there was no systematic motion error included.

Proton Treatment Planning

The passive-scattered proton plans were planned using the XiO TPS (v4.2.1, CMS Software). In passive-scattered proton radiotherapy, each beam delivers a homogenous dose to the target volume. To spread-out the dose to normal tissues each plan consists of at least two, but preferably three, beam directions. Although range uncertainties and setup errors are taken into account in the treatment planning process, the use of multiple beam directions minimizes the risk of underdosing the target due to unexpected density variations, for example, heavy breathing or a substantial change in the average tumor position with respect to the patient anatomy as used for treatment planning.

Given a midventilation CT scan of the tumor and a description of the breathing-induced excursion from this position in all three directions, treatment planning of proton radiotherapy at MGH is a two-step process. As we may choose to treat only a subset of fields on any given treatment

day, it is important that each field separately ensures target coverage.

First, for each beam, we conform the 95% isodose level as closely as possible to the target, that is, the CTV. The aperture shape for each beam is chosen to conform the 95% isodose level in all lateral directions. The proton beam range and range compensator are chosen to conform distally (downstream) to the target volume. The radiological "thickness" of the target (in the depth direction) determines the choice of modulation width of the spread-out Bragg peak. In our center, we employ M_{98} for the definition of modulation, that is, the distance between the proximal 98% and the distal 90% isodose level. Because of the nature of passive-scattered proton radiotherapy, tight proximal coverage cannot be achieved except for those regions where the radiological thickness equals the maximum thickness.

Second, margins were applied to the aperture, the range compensator, and both the range and modulation width. Range uncertainties of 3.5% and 1 mm were applied.[63] The same range uncertainty to the modulation width was applied, taking into account that the increase in range already translated into an increase in necessary modulation width. For example, a field with a range of 16 cm and modulation of 10 cm after step one will have a range and modulation width of 16.8 and 11.2 cm, respectively.

Aperture expansion and range compensator smearing was applied,[64] meaning that the safety margin is typically less than the summation of setup error and half the peak-to-peak breathing amplitude. Aperture expansion (i.e., lateral margining) compensates for setup errors of the tumor in the lateral direction with respect to the central beam axis. Range compensator smearing (i.e., distal margining) is applied to take into account the effect of the shift in the patient density distribution and the detrimental effects of these density variations on distal target coverage. The overshoot due to smearing depends on the local variation in the range compensator thickness and hence is not uniform across the lateral extent of a field. The exact magnitude of lateral and distal margining depends on the extent of the breathing motion but will never be less than the expected maximum setup error, refer to Table A1.

Our TPS only allows a single uniform value for smearing on a per range compensator basis. Lateral aperture margins differed depending on the breathing motion in a specific direction. All patients' plans consisted of fields in the transversal plane only.

Conformity Index

Assessment of the differences in conformity when comparing treatment plans from different modalities has been published before.[30] To compare target coverage and unwanted dose to the noncritical as well as the critical normal tissue (OARs), we chose to use the "conformation number" (CN).[31]

The CN takes into account the quality of tumor irradiation as indicated by the first part of the equation (Eq. A2) and the irradiation of the noncritical tissue, indicated by the second part.

$$CN_{T,ref} = \frac{V_{T,ref}}{V_T} \times \frac{V_{T,ref}}{V_{ref}} \quad \text{(A2)}$$

where $V_{T,ref}$ is the volume of the target receiving a dose equal to or greater than the reference dose, V_T is the volume of the target, and V_{ref} is the overall volume receiving a dose equal to or greater than the reference dose or target dose.[29] The reference dose was chosen to be 95% of the PD to the PTV and the CTV was again chosen as the target volume. For clarity, the CN can thus be written as follows in our case:

$$CN = \frac{CTV_{95}}{CTV} \times \frac{CTV_{95}}{V_{95}} \quad \text{(A2)}$$

TABLE A1. Safety Margin as a Function of the Setup Error and the Peak-to-Peak Breathing Amplitude

Setup Error (mm)	Breathing Amplitude (mm)	Safety Margin (mm)
5	0	5
5	5	6
5	10	7
5	20	8

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